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Manufacturing method of a diphosphoglyceric acid salt.

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Fair Copy of Specifications (No Revisions to the Contents)

Specifications

1 Description of Invention

Manufacturing method of a diphosphoglyceric acid salt.

2 Scope of Patent Claim

The production of an organic amine salt from 2,3-diphosphoglyceric acid by the reaction of 2.6-bis-(diethanolamino)-4,8-dipiperidinopyrimido-(5.4-d)-pyrimidine with 2,3-diphosphoglyceric acid.

3 Detailed Explanation of Invention

2,3-diphosphoglyceric acid is widely distributed in microbes, plants and mammals, specifically, high numbers are found in the red blood cells of mammalian species.

This invention produces a new type of organic amine salt of 2,3-diphosphoglyceric acid that exhibit similar activity by reacting 2.6-bis-(diethanolamino)-4,8-dipiperidinopyrimido-(5.4-d)-pyrimidine with 2,3-diphosphoglyceric acid.

The organic amine salt of 2,3-diphosphoglyceric acid obtained by this invention is a new chemical compound. Its physiologically active effects (especially effects related to prevention of thrombus formation) are made stronger through a synergistic action than those same effects produced by 2,3-diphosphoglyceric acid. It is extremely useful as a drug for the medical treatment of arterial thrombosis, angina pectoris, and related arterial diseases, as well as medicaments that act in the prevention of blood clots associated with hemodialysis.

The chemical properties of the organic amine salt of 2,3-diphosphoglyceric acid produced by the invention are shown in Table 1.

Table 1.

Name of Base	Molecular Formula	Analytical Values (N%)	
		Theoretical Value	Observed Value
2.6-bis-(diethanolamino)-4,8-dipiperidinopyrimido-(5.4-d)-pyrimidine	$C_{37}H_{48}N_{16}P_8O_{16}$	1455	1503

The following illustrates the platelet aggregation suppression effect of the chemical compound produced by this invention.
Changes in transmission levels observed using an Aggregometer are shown in Graph 1.
In a round cuvette, 0.8ml of marmot Platelet Rich Plasma (PRP) was added along with 0.1ml of either the test solution or 0.1ml saline (used as a control), producing a total volume of 1.0 ml.
Measurements were taken at 37°C and approximately 3000ppm under agitation.
According to the invention, the chemical compound produced show an excellent platelet aggregation suppression effect. The effect are shown to be strikingly higher than that of both a 2,3-diphosphoglyceric acid and a salt of 2.6-bis-(diethanolamino)-4,8-dipiperidinopyrimido-(5.4-d)-pyrimidine.

Further detailed explanation of the invention with recourse to a practical example is shown below.

Practical Example 1

5g of 2.6-bis-(diethanolamino)-4,8-dipiperidinopyrimido-(5.4-d)-pyrimidine is dissolved in 10ml of ethanol. When an ethanol solution containing 3g 2,3-diphosphoglyceric acid is added to this solution yellow-orange crystals are precipitated. When recrystallized from a large quantity of ethanol, 6g 2.6-bis-(diethanolamino)-4,8-dipiperidinopyrimido-(5.4-d)-pyrimidine salt of 2,3-diphosphoglyceric acid with a melting point of 250°C and above (characteristic resolution) is obtained in the form of yellow crystals.

4. Simple Explanation of the Graph

Marmot platelet suppression activity as related to the salt of 2.6-bis-(diethanolamino)-4,8-dipiperidinopyrimido-(5.4-d)-pyrimidine from 2,3-diphosphoglyceric acid is shown in Graph 1.
Shown in graph, 1 is the control, 2 is 2,3-diphosphoglyceric acid (50μg), 3 is 2.6-bis-(diethanolamino)-4,8-dipiperidinopyrimido-(5.4-d)-pyrimidine (100μg) and 4 is the salt of 2.6-bis-(diethanolamino)-4,8-dipiperidinopyrimido-(5.4-d)-pyrimidine (50μg) from diphosphoglyceric acid.
The arrow indicates the point at which norepinepherine (5μM) was added.

Graph 1
X-AXIS-MINUTES
Y-AXIS-TRANSMISSION LEVEL

Protocol Amendments (Formula)

Commisionner of Patents Kawabara, Norio

1. Case Designation Showa 55 Patent Application Number 6.507

2. Description of Invention

Manufacturing method of a diphosphoglyceric acid salt.

3. Amendment Requester

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5. Amendment Order Date May 27, 1980 (postmark)

6. Object of Amendment

Application Form and Written Details

7. Content of Amendment

Application and Fair Copy of Specifications (no change to the contents)